UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,185	08/03/2005	Gordon D. Ross	3593.1001-008	6460

21005 7590 03/23/2010

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.
530 VIRGINIA ROAD
P.O. BOX 9133
CONCORD, MA 01742-9133

EXAMINER	
RICCI, CRAIG D	

ART UNIT	PAPER NUMBER
1628	

MAIL DATE	DELIVERY MODE
03/23/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,185	ROSS ET AL.	
	Examiner	Art Unit	
	CRAIG RICCI	1628	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,14 and 16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 14, and 16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendments filed 10/15/2009 were entered.

Response to Arguments

2. Applicants' arguments, filed 10/15/2009, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. **Claims 1 and 4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of suppressing or eliminating tumor cells in a subject in need thereof, wherein the composition comprises: (a) a neutral soluble glucan; and (b) an antibody (e.g., direct administration of a monoclonal or polyclonal antibody), does not reasonably provide enablement for of suppressing or eliminating tumor cells comprising administering (a) a neutral soluble glucan; and (b) a vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims**.

5. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

6. Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue

experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

7. **The nature of the invention**: The instant claims read on a method to suppress or eliminate tumor cells in a subject in need thereof, comprising administering to said subject (a) a neutral soluble glucan; and (b) a vaccine (see Specification, Page 5, Lines 28-31). The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

8. **Level of skill in the art**: The level of skill in the art is deemed to be high, generally that of a PhD or MD.

9. **The breadth of the claims**: The instant claims read on a method to suppress or eliminate tumor cells in a subject in need thereof, comprising administering to said subject (a) a neutral soluble glucan; and (b) a vaccine. The term "vaccine" encompasses the ability of a specific antigen to induce protective immunity to cancer. In short, the claims encompass a method of

eliminating, e.g., preventing, tumor cells in a subject in need thereof comprising administering a vaccine, i.e., a prophylactic.

10. **Guidance in the specification and Working Example**: The specification provides a data demonstrating the administration of (a) a neutral soluble glucan; and (b) an antibody (e.g., direct administration of a monoclonal or polyclonal antibody) reduces tumor formation in mice (e.g., Page 62, Example 3). Thus, while the specification appears to suggest that the administration of (a) a neutral soluble glucan; and (b) an antibody (e.g., direct administration of a monoclonal or polyclonal antibody) is therapeutically effective for the treatment of cancer, one cannot extrapolate the teachings of the specification to the scope of the claims because the specification provides no exemplification or guidance on how to use the claimed administration of a vaccine for protective purposes with any predictability. With regards to tumor immunotherapy, the goal of tumor vaccination is the induction of tumor immunity to prevent tumor recurrence and to eliminate residual disease. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the cancer prevention, is required for practice of the claimed invention.

11. **Quantity of experimentation**: The quantity of experimentation in the areas of cancer therapy is extremely large given the unpredictability associated with protecting an animal against cancer given the fact that no known cure or preventive regimen is currently available for cancer.

12. **The unpredictability of the art and the state of the prior art**: Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer.

This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. The prevention of cancer, let alone the prevention of cancer with a vaccine, is highly unpredictable. The majority of studies suggest that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in *advance* of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. Further, such studies require the appropriate experimental models for analyzing chemo- or immunoprevention. For example, *Granziero et al.* (Eur. J. Immunol. 1999, 29:1127-1138) teach that many models are not suitable for testing immunotherapeutic approaches intended to cure cancer. They suggest that the optimal model (prostate cancer, in their case) would have spontaneous tumor development in its natural location (1st column, page 1128) wherein disease progression would closely resemble the progression of the particular type of cancer. Hence, depending on the type of model employed one could establish a reasonable link between antecedent drug and subsequent knowledge of the prevention of the disease. Further, reasonable guidance with respect to correlating agents that prevent cancer may depend upon quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. For example, *Byers, T.* (CA Journal, Vol. 49, No. 6, Nov/Dec. 1999) teaches that randomized

controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, *Byers* suggests that chemo-preventative trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably prevent the formation of tumors in a mammal. This, combined with the state of the art of preventing cancer, suggests that undue experimentation would be required to practice the invention as broadly claimed. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. While a few vaccines designed to prevent cancer by preventing a precursor infection are in common use or in the latter stages of clinical development, (*Frazer, I.* (Expert. Opin. Pharmacother. 2004; 5: 2427-2434)), a recent review of such vaccines did not indicate nor suggest that such therapies would be successful in the prevention of cancer not triggered by infection. For example, *Frazer, L.* discloses that the induction of an antibody to a tumor-specific membrane protein is not feasible because the level of the antibody required for protection is undefined, requires large doses of MAbs and the tumor specific antigens are not on the cells or are also secreted in significant quantity (page 2431, 2nd column, last paragraph). *Frazer* further discloses (page 2431, 2nd column, last paragraph to page 2432) caveats of immunoprophylaxis based on the induction of a T-cell mediated immune response to a tumor specific antigen. For instance, *Frazer* discloses that some of these caveats include: (1) establishing an autoimmune disease if the tumor antigen is also expressed on non tumor cells; (2) vaccines developed to induce memory T cells are not

likely to become reactivated to become effector cells even when the tumor antigen is being produced by the tumor because cross-presentation of tumor antigens to the memory T cell population by professional antigen-presenting cells to generate effector cells is rather poor when compared with presentation following immunization; and (3) even if the antigen is effectively cross presented, many evolving tumors, like the "normal" cells they have evolved from, present antigen directly in an anti-inflammatory and immunosuppressive environment, through secretion or anti-inflammatory cytokines, such that the tumor cells are unlikely to attract the attention of any induced circulating effector cells.

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. **Claims 1-4, 14, and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Vetvicka et al* (cited in a previous Action), *Jamas et al* (cited in a previous Action),**

***Hortobagyi* (cited in a previous Action), *Sliwkowski* (cited in a previous Action) as evidenced by *Gelderman et al* (cited in a previous Action), and *Kolb et al* (cited in a previous Action).**

16. As amended, instant claim 1 is drawn to a method of suppressing or eliminating tumor cells, comprising administering to a subject in need of suppressing or eliminating tumor cells a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells, wherein the glucan does not induce systemic release of inflammatory cytokines and the glucan and antibody together suppress or eliminate tumor cells.

17. As discussed in the previous Action mailed on 4/15/2009, and reiterated largely as follows, it is well known in the art, as evidenced by *Vetvicka et al*, that iC3b-coated tumor cells are not targeted for destruction by natural killer cells (Page 50, Column 2). However, soluble β-glucans cause natural killer (NK) cells "to express potent tumoricidal activity" (Page 50, Column 2) by "priming" the CR3 receptors of NK cells "for cytotoxicity of iC3b-tumor cells that were otherwise resistant to killing" (Page 51, Column 1). Notably, *Vetvicka et al* also disclose that "[e]xperiments have now shown that the density of bound iC3b/C3dg on freshly isolated breast tumors is adequate for *in vitro* recognition and cytotoxicity of SZP-primed CR3. In experiments with mice, SZP therapy caused regression of established mammary tumors" (Page 59, Column 2). Thus, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer soluble β-glucans to suppress or eliminate mammary tumor cells to a subject in need thereof in view of *Vetvicka et al*. The skilled artisan would have been motivated to do since *Vetvicka et al* teach that (1) soluble β-glucans prime NK cells for cytotoxicity of iC3b-tumor cells; (2) mammary carcinoma cells contain sufficient iC3b for

recognition by CR3-primed NK cells; and (3) STZ (which similarly primes CR3 of NK cells (Page 59, Column 2)) can treat mammary tumors. Accordingly, the skilled artisan would have reasonably predicted that administration of soluble β-glucans would prime CR3 of NK cells for cytotoxicity of iC3b-tumor cells and specifically mammary carcinoma cells, thus treating mammary tumors.

18. However, *Vetvicka et al* do not explicitly teach the administration of **neutral** soluble glucans as recited by instant claim 1. Nor do *Vetvicka et al* teach the administration of at least one complement activating anti-tumor antibody as recited by instant claim 1.

19. **FIRST**, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer neutral soluble glucans, specifically, as opposed to soluble glucans (as taught by *Vetvicka et al*) in view of *Jamas et al*. *Jamas et al* disclose that the administration of soluble β-glucans (but not neutral soluble glucans) stimulate cytokines such as tumor necrosis factor (Column 2, Lines 39-55) which is "involved in infection, inflammation and **cancer**" (Column 3, Lines 14-15, emphasis added). As such, it would have been *prima facie* obvious to administer **neutral** soluble glucans (as taught by *Jamas et al*) instead of soluble glucans to suppress or eliminate mammary tumor cells (as taught by *Vetvicka et al*). The skilled artisan would have been motivated to do so in order to prime NK cells for cytotoxicity of iC3b-tumor cells (e.g., mammary tumor cells) while avoiding the adverse side affects caused by the stimulation of tumor necrosis factor (i.e., cancer) with a reasonable expectation of success considering that *Jamas et al* specifically teach that neutral soluble glucans retain "a specific subset of immunological properties common to β-glucans but uniquely do not induce production of IL-1 and TNF *in vitro* or *in vivo*" (Column 3, Lines 45-48). As such, it is asserted that the

glucan would not induce systemic release of inflammatory cytokines as recited by claim 1 as amended.

20. **SECOND**, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to also administer at least one complement activating anti-tumor antibody as recited by claim 1 for each of the following reasons: **(1)** complement activating anti-tumor antibodies, such as trastuzumab (a monoclonal antibody), are well known in the art for the treatment of cancer, including mammary carcinoma, as evidenced by *Hortobagyi* (Abstract). As stated in MPEP 2144.06, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose… [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626, F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to also administer at least one complement activating anti-tumor antibody, specifically trastuzumab, in view of *In re Kerkhoven*, with a reasonable expectation of success. And **(2)**, *Sliwkowski* et al teach that trastuzumab activates complement, as evidenced by *Gelderman et al* (Page 160, Column 1, Reference 15). Since iC3b is generated during activation of the complement system (as evidenced by *Kolb et al* (Column 3, Lines 3-8)), the skilled artisan would have reasonably predicted that the co-administration of trastuzumab would promote iC3b coating of tumor cells, thus enhancing the targeting of neutral soluble glucan CR3-primed NK cells for cytotoxicity of the iC3b-coated tumor cells. Accordingly, it would have been *prima facie*

obvious to a person of ordinary skill in the art to administer a neutral soluble glucan and at least one complement activating anti-tumor antibody (trastuzumab) to a subject in need thereof.

21. Thus, for all of the foregoing reasons, instant claims 1-3 and 16-18 are rejected.

22. Applicant, however, argues that the suggested combination of documents fails to provide the required level of predictability because one could not have administered the claimed compositions to a subject and predictably obtained the enhanced anti-tumor activity compared to administering either component alone (Applicant Argument, Page 11). Applicant further argues that *In re Kerkhoven* can not apply to biological systems where "one cannot automatically predict that two components... can form a combined composition useful for the same purpose" (Applicant Argument, Pages 11-12). And, finally, Applicant argues that "[t]he fact that complement activating anti-tumor antibody and the neutral soluble glucan both activate complement to achieve their respective anti-tumor effects means that the combination may not necessarily have an additive effect. Indeed, the combination may have reduced activity" (Applicant Argument, Page 12).

23. Applicants are reminded that obviousness does not require absolute predictability, only a reasonable expectation of success of obtaining similar properties. *In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). In the instant case, it would have been reasonable to expect that the combination of agents would have an additive effect in view of "[t]he fact that complement activating anti-tumor antibody and the neutral soluble glucan both activate complement to achieve their respective anti-tumor effects". Furthermore, there is nothing to support Applicant's contention that *Kerkhoven* is not applicable to biological systems or that one of skill in the art

would have expected the combination to provide reduced activity. The arguments of counsel can not take the place of evidence in the record. See *In re Schulze*, 346 F.2d 600 (CCPA 1965).

24. For the foregoing reasons, Applicant's arguments are not considered persuasive. The rejection of claims is maintained. Since Applicant did not traverse the rejection of claims 4 and 14 beyond the grounds already discussed above, the rejection of claims 4 and 14 is also maintained, as follows:

25. Instant claim 4 is drawn to the method of claim 1 wherein the soluble beta glucan is administered parenterally. As disclosed by *Jamas et al*, "[t]he neutral soluble glucan preparation is appropriate for parenteral... administration" (Column 4, Lines 1-3). Accordingly, it would have been *prima facie* obvious to a person of ordinary skill in the art to administer the soluble beta glucan is parenterally

26. Instant claim 14 is drawn to the method of claim 1 wherein the neutral soluble glucan is in a single and/or triple helix conformation. Significantly, the neutral soluble glucans taught by *Jamas et al* are in the triple helix conformation (Column 3, Lines 54-55).

27. **Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cheung* (US 7,462,607 which claims benefit of 60/261,911 filed 1/16/2001) in view of *Jamas et al* (cited in a previous Action)**

28. As discussed above, instant claim 1 is drawn to a method of suppressing or eliminating tumor cells comprising administering to a subject in need of suppressing or eliminating tumor cells a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells (specifically, rituximab (claim 3) introduced via direct administration (claim 2)), wherein the glucan does not induce systemic

release of inflammatory cytokines and the glucan and antibody together suppress or eliminate tumor cells.

29. *Cheung* teaches a method of suppressing or eliminating tumor cells or regressing tumor growth (including breast cancer (Column 2, Line 31)) comprising administering a subject in need thereof Barley beta-glucan (which is a soluble glucan) and direct administration of 3F8 (which is a complement activating anti-tumor antibody) (Column 3, Lines 20-38). Furthermore, *Cheung* discloses that in another embodiment, the antibody is rituximab.

30. However, *Cheung* does not disclose administering a ***neutral*** soluble glucan wherein the glucan does not induce systemic release of inflammatory cytokines.

31. As discussed above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer ***neutral*** soluble glucans, specifically, as opposed to soluble glucans in view of *Jamas et al*. *Jamas et al* disclose that the administration of soluble β-glucans (but not ***neutral*** soluble glucans) stimulate cytokines such as tumor necrosis factor (Column 2, Lines 39-55) which is "involved in infection, inflammation and **cancer**" (Column 3, Lines 14-15, emphasis added). As such, it would have been *prima facie* obvious to administer **neutral** soluble glucans (as taught by *Jamas et al*) instead of soluble glucans to suppress or eliminate mammary tumor cells in the invention taught by *Cheung*. The skilled artisan would have been motivated to do so in order to treat cancer without stimulating cytokines with a reasonable expectation of success.

32. Accordingly, instant claims 1-3 are rejected as *prima facie* obvious.

33. **Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Cheung* (US 7,507,724 which claims benefit of 60/261,911 filed 1/16/2001) in view of *Jamas et al* (cited in a previous Action)**

34. As discussed above, instant claim 1 is drawn to a method of suppressing or eliminating tumor cells comprising administering to a subject in need of suppressing or eliminating tumor cells a neutral soluble glucan and at least one complement activating anti-tumor antibody directed to the tumor cells or antigens of said tumor cells (specifically, rituximab (claim 3) introduced via direct administration (claim 2)), wherein the glucan does not induce systemic release of inflammatory cytokines and the glucan and antibody together suppress or eliminate tumor cells.

35. *Cheung* teaches a method of suppressing or eliminating tumor cells or regressing tumor growth (including breast cancer (Column 2, Line 31)) comprising administering a subject in need thereof Barley beta-glucan (which is a soluble glucan) and direct administration of 3F8 (which is a complement activating anti-tumor antibody) (Column 3, Lines 20-38). Furthermore, *Cheung* discloses that in another embodiment, the antibody is rituximab.

36. However, *Cheung* does not disclose administering a ***neutral*** soluble glucan wherein the glucan does not induce systemic release of inflammatory cytokines.

37. As discussed above, it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to administer ***neutral*** soluble glucans, specifically, as opposed to soluble glucans in view of *Jamas et al*. *Jamas et al* disclose that the administration of soluble β-glucans (but not ***neutral*** soluble glucans) stimulate cytokines such as tumor necrosis factor (Column 2, Lines 39-55) which is "involved in infection, inflammation and

cancer" (Column 3, Lines 14-15, emphasis added). As such, it would have been *prima facie* obvious to administer **neutral** soluble glucans (as taught by *Jamas et al*) instead of soluble glucans to suppress or eliminate mammary tumor cells in the invention taught by *Cheung*. The skilled artisan would have been motivated to do so in order to treat cancer without stimulating cytokines with a reasonable expectation of success.

38. Accordingly, instant claims 1-3 are rejected as *prima facie* obvious.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CRAIG RICCI whose telephone number is (571) 270-5864. The examiner can normally be reached on Monday through Thursday, and every other Friday, 7:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Padmanabhan "Paddy" Sreenivasan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/CRAIG RICCI/
Examiner, Art Unit 1628

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642